II. REMARKS

A. Status of the Claims

Claims 1-11 and 24-37 were pending in the case at the time of the Office Action. Claims 1, 5-9, 24, and 30-34 have been amended in the Amendment set forth herein. No claims have been canceled. New claims 38-51 have been added. Therefore, claims 1-11 and 24-51 are currently under consideration.

Claims 1, 5-9, 24, and 30-37 have been amended to recite that the self protein is a hormone. New claims 38-44 depend from claim 5, and recite specific hormones. New claims 45-51 depend from claim 30, and recite specific hormones. Support for the Amendments to the claims and the new claims can be found generally throughout the specification, such as in the claims as originally filed and page 4, lines 7-18.

B. The Rejections Under 35 U.S.C. §112, First Paragraph, Are Overcome

Claims 1-11 and 24-36 are rejected under 35 U.S.C. §112, first paragraph, because the specification is said to not be enabling for the full scope of the claims. The Examiner argues that while the specification is enabling for methods and processes for increasing the circulating level of a self protein that is erythropoietin or a growth hormone that undergoes secretion, diffusion or transport to the circulation upon expression *in vivo*, it is said to not be enabling for the full scope of the claims. Applicants respectfully traverse.

Applicant reminds the Examiner that the test of enablement is whether the disclosure, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention without undue experimentation. See *Manual of Patent Examining Procedure (MPEP)* §2164.01. The Examiner

appears to argue that because the instant specification does not teach a use of the invention other than for gene therapy, that the claims are not enabled for such other applications by the instant specification. The specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation. *MPEP* §2164.02, citing *In re Borkowski*, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970). One of ordinary skill in the art would be able to practice the claimed method in contexts that do not pertain to gene therapy without undue experimentation in view of the disclosure set forth herein.

Applicants note that their specification is fully enabling for the full scope of the claims as written. Information regarding proteins present in the circulation of an animal can be found, for example, on page 4, lines 8-18. Information regarding viral vectors that can be applied in the context of the present invention can be found, for example, on page 5, lines 3 – page 8, line 25 and page 10, line 3 – page 11, line 14. Information regarding *in vivo* and *ex vivo* transformation of muscle cells can be found generally throughout the specification, such as on page 11, line 15 – page 12, line 7. Detailed information regarding processes for increasing the circulating levels of a self protein in the blood stream of an immunocompetent animal that involve delivery of viral vectors *in vivo* to muscle cells can be found throughout the specification, such as in working Examples 5-10 (page 16, line 11 - page 23, line 6). Further, the information pertaining to use of plasmid vectors set forth in Examples 1-4 of the specification provides additional detail that can be applied by one of ordinary skill in the art in the practice of the claimed methods. Further, the data set forth in the specification demonstrates that the processes that are claimed result in stable long-term expression of a self-protein in an immunocompetent subject.

The Examiner argues that the specification does not provide guidance as to how the claimed processes can be used in the treatment of disease in an animal, and that the specification does not teach the level of gene expression required, the number of transduced cells needed, when or for how long the gene should be expressed, or the frequency of administration of the gene therapy vector required, for treatment of any pathological condition. Applicant disagrees.

The specification provides detailed guidance to one of ordinary skill in the art regarding treatment of disease. For example, page 6, lines 9-11 clearly indicate that the results set forth in the specification can be safely and effectively applied to treat patients with Epo-responsive anemias. Furthermore, the background section on pages 1-2 of the specification clearly delineates that diseases contemplated for treatment by the present invention include those diseases associated with "inherited and acquired serum protein deficiencies including hemophilia A, diabetes mellitus, and erythropoietin-responsive anemias," to name a few examples. Specification, page 1, lines 13-16. Applicant is not required to explicitly recite every disease that can be treated using the processes of the present invention. The state of the art pertaining the level of understanding pertaining to diseases associated with protein deficiencies was high at the priority date; no evidence to the contrary has been submitted by the Examiner.

The burden of setting forth a *prima facie* case of unpatentability under 35 U.S.C. §112, first paragraph, is with the Examiner. See *MPEP* §2164.04. The Examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure. *Id.* Here, the Examiner concedes that the specification is enabling for increasing the circulating levels of erythropoietin but not for other self proteins. No reasonable basis has been set forth to establish that one of ordinary skill in the art would not be

able to apply the information set forth in the specification to increasing the circulating level of other hormones, and applying the claimed methods to the treatment of disease.

Regarding the Examiner's assertion that the specification provides insufficient guidance pertaining to the level of gene expression required, the number of transduced cells needed, when or for how long the gene should be expressed, Applicants note that specific guidance in the context of erythropoietin is provided on page 6, lines 1 – page 8, lines 25. Detailed information is set forth in this section regarding dosage of viral vector in animals, and effect of dose modification on serum erythropoietin level and hematocrit. In view of the specific and detailed guidance set forth herein pertaining to erythropoietin, one of ordinary skill in the art would be able to apply this information in a process for increasing the serum level of any other hormone. No reasonable basis to doubt this ability has been set forth by the Examiner. *See In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) (In order to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided by the claimed invention).

Here, the Examiner argues that the specification does not provide any guidance as to "the use of the claimed DNA methods to treat a diseased animal" because "[t]he specification does not teach the level of gene expression required, the number of transduced cells needed, when or for how long the gene should be expressed, or the frequency of administration of the gene therapy vector required." Office Action, page 4. Regarding the level of gene expression required, Applicants note that the claims are directed to processes and methods for increasing the circulating level of a hormone in the blood stream of an immunocompetent animal. If expression of such gene is not increased, then the process or method falls outside of the scope of the claimed invention. Regarding the question as to how much of an increase in the circulating level of a

hormone should be sufficient to treat a disease, Applicants respectfully submit that determining a response to therapy and determining how much of an expression of a gene may be sufficient to result in a therapeutic response falls within the level of ordinary skill of one of ordinary skill in the art. If, for example, an increase in circulating level of a hormone is not sufficient to result in a therapeutic effect, then the clinician of ordinary skill would understand that, for example, a repeat administration of transformed muscle cells may be required. Each of the issues set forth by the Examiner, including when and for how long a gene should be expressed, are questions which are readily addressed by those of ordinary skill in the art. While some assessment may be required to optimize the method to result in a therapeutic effect, no reasonable basis has been set forth by the Examiner to establish that any undue experimentation would be required to optimize dose to result in a therapeutic response.

Applicants disagree with the Examiner's statement that "[a]t the time the application was filed, the art of administering any type of genetic expression vector to an individual so as to provide a tangible therapeutic benefit was poorly developed and unpredicable." Office Action, page 5. Applicants previously submitted a review article published around the time of the priority date (Svensson *et al.*, Molecular Medicine Today, April 1996, pp. 166-172; hereinafter "Svensson"; Exhibit 1 of response to Office Action dated February 13, 2007) which provides as follows:

> **"The past five years have witnessed tremendous growth in the field of gene therapy, with pre-clinical and clinical gene therapy trials for diseases as diverse as cancer, AIDS, and atherosclerosis. These studies have utilized many different vectors and target organs in order to achieve therapeutic effects."**

Svensson proceeds to provide an overview of the state of the art regarding ***muscle-based gene therapy***, including the state of the art pertaining to myoblast transplantation (page 167-168), direct DNA injection (page 168), adenovirus vectors (page 168-169), and other vector systems

for muscle based gene therapy (page 169). Furthermore, there was discussion regarding diseases that can be targeted using gene-based therapy (pages 169-170). Thus, contrary to the Examiner's assertion, the state of the art was not so very poorly developed and unpredictable in the field of the invention. It was clearly sufficiently advanced such that a person of ordinary skill in the art, when presented with the information set forth in the specification, would have been able to practice the claimed invention without an undue amount of experimentation.

As further evidence that the claimed methods can be used in gene therapy applications to produce a therapeutic effect, Applicant previously submitted the following Exhibits:

- Wang and Herzog, "AAV-Mediated Gene Transfer for Treatment of Hemophilia," Current Gene Therapy, 2005, 5, 349-360 (Exhibit 2 of response to Office Action dated Feb. 13, 2007). This report presents an overview of the state of the art pertaining to AAV-mediated factor IX gene transfer to skeletal muscle of animals and humans.

- Kay *et al.*, "Evidence for gene transfer and expression of Factor IX in haemophilia B patients treated with an AAV vector. Nat. Genet. (2000), 24:257-261 (Exhibit 3 of response to Office Action dated Feb. 13, 2007).

- Manno *et al.*, "AAV-mediated Factor IX gene transfer to skeletal muscle in patients with severe hemophilia B." Blood (2003) 101:2963-2972 (Exhibit 4 of response to Office Action dated Feb. 13, 2007).

These references are not cited to show the state of the art at the time the present application was filed, but are cited to demonstrate that the present specification as written is enabling for the scope of the claims, and to demonstrate that the claimed methods can in fact be used in gene

therapy applications. These references do not establish that undue experimentation would be required to practice the claimed methods. The Examiner writes that "absent any showing that the claimed methods can be used in gene therapy applications to produce the intended therapeutic effect, the claims directed to methods for gene therapy are not enabled by the disclosure." Office Action, page 5. Applicants disagree, again directing the Examiner to the above references which further support that the specification as written enables the claims for their full scope.

The quotes that the Examiner refers to in describing pessimism in the field of gene therapy are not indicative of enablement in the state of the art pertaining to muscle-based gene therapy. The references cited by the Examiner do not indicate that one of ordinary skill in the art would not be able to apply a method to increase the circulating level of a hormone to treat a disease. At most, the quotes cited by the Examiner on pages 5-6 of the Office Action merely suggest that continued effort should continue to improve gene therapy technology.

Regarding Rubanyi, cited by the Examiner in the paragraph bridging pages 5-6 of the Action, it is noted in the abstract that gene therapy prerequisites for success include therapeutically suitable genes, appropriate gene delivery systems, and proof or principle of efficacy and safety in appropriate clinical models. The instant specification establishes each of these factors, and the methods of the present invention have found application in the treatment of disease. The examples provided in the specification can be applied in providing guidance to one of ordinary skill in the art, particularly in view of the state of the art pertaining to muscle-based gene therapy, to apply the claimed invention to increase serum levels of a protein to treat a disease. Thus, while it may be possible that some experimentation may be required to practice the claimed invention in some embodiments, no sufficient evidence has been set forth by the

Examiner to show that any such experimentation would be undue experimentation. See *MPEP* §2164.06.

Regarding new claims 38-51, their either depend from claim 5 or claim 30, which for the reasons discussed above are sufficiently enabled by the present specification.

In view of the foregoing, each of the pending claims is enabled by the instant specification. Regarding new claim 37, it depends from claim 1, which for the reasons discussed above is enabled by the instant specification. Therefore, it is respectfully requested that the enablement rejection under 35 U.S.C. §112, first paragraph, should be withdrawn.

C. Conclusion

In view of the foregoing, it is respectfully submitted that each of the pending claims is in condition for allowance, and a Notice of Allowance is earnestly solicited. The Examiner is invited to contact the undersigned attorney at (512) 536-5639 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,

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